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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,305	06/19/2003	Mark Zylka	CALTE.015A	5172

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/14/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/601,305	ZYLKA ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 12-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments

The Amendment filed on 12/27/06 in response to the previous Non-Final Office Action (10/25/06) is acknowledged and has been entered.

Claims 1-22 are pending. Claims 9, 10, 12-16 are previously withdrawn for non-elected invention. Claims 1-8, 11, 17-22 are under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

The following office action contains NEW GROUNDS of rejection.

Rejections/Objections Withdrawn

The objection of drawing figure 3, 4, and 5 is withdrawn in view of the amendments to the specification by adding illustration of the figures in paragraph [0016]-[0018].

Response to Arguments

Rejection under 35 USC § 101/112 1st

The rejection of claims 1-8, 11, and 17-22 remain rejected under 35 U.S.C. 101 and 112 1st paragraph because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility as stated below.

> Claims are drawn to a method of diagnosing skin cancer comprising melanoma by detecting the expression of MrgX2 protein (SEQ ID NO: 4) in the tissue or cell samples, where in the MrgX2 expression is determined by contacting the tissue sample with an antibody comprising labeled monoclonal antibody that specifically binds to the tissue sample or by contacting the an antibody to the protein isolated from tissue sample.
>
> In order to fulfill the requirements of 35 U.S.C. 101, said binding must be indicative of a specific, substantial and credible utility, such as the diagnosis of a pathological condition. The specification teaches MrgX2 protein comprising amino acid sequence SEQ ID NO: 4 (para 13). The specification teaches antibody to MrgX2 protein (page 12-13). The specification teaches that MrgX2 RNA is exclusively expressed in melanoma cell lines, not in other tissues (table 2, page 45 and figure 5). Although the specification teach a general method used in the art for diagnosing melanoma by antibodies to human MrgX2 protein, the specification does not teach whether the levels of MrgX2 protein, as opposed to the polynucleotides (RNA) encoding said protein, in the melanoma cells or tissues samples are higher than normal skin tissues. The specification does not provide any objective evidence on the expression of MrgX2 protein in either melanoma tissue,

melanoma cell, or any normal tissues samples. The specification teaches neither the expression of MrgX2 protein (SEQ ID NO: 4) by any primary or invasive/metastasis melanoma cells, nor binding of an antibody to melanoma cells, which express MrgX2 protein.

Therefore, the specification only provides an evidence of the expression of MrgX2 in the melanoma and normal samples by showing the levels of the message RNA (mRNA). The specification does not provide any teaching on whether the protein expression is correlated with the levels of mRNA in any of these tissues or cells. The art recognizes that expression of mRNA neither dictate nor predict the translation of such mRNA into a polypeptide. For examples, the abstract of Brennan et al., (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. The abstract of Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. The abstract of Powell et al., (Pharmacogenetics, 1998, Vol. 8, pp. 411-421) teaches that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. In this event although the mRNA of MrgX2 was demonstrated to be expressed in melanoma, according the teachings in the art, said demonstration cannot be relied upon to anticipate that MrgX2 protein of SEQ ID NO: 4 would be similarly expressed in same cancer cells.

More evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels are following: The abstract of Hell et al., (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teaches that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. The abstract of Carrere et al., (Gut, 1999, vol. 44, pp. 545-551) teaches an absence of correlation between protein and mRNA levels for the Reg protein. The abstract of Guo et al., (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teaches that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both transcriptional and post-translational level. These references serve to demonstrate that levels polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, the abstract of Jang et al., (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teaches that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

Since there is not evidence showing the expression of MrgX2 protein (SEQ ID NO: 4) in melanoma tissue or cells, the antibody to the protein would not bind to the melanoma tissue or cells, which express only mRNA of MrgX2. Since the specification has not correlated the claimed method of binding an antibody to a melanoma tissue or cells with the expression of mRNA in (not a protein) in the cells, instant method claims recite diagnosing a skin cancer including melanoma in a patient comprising determining the levels of expressing MrgX2 protein (SEQ ID NO:4) by binding an antibody to human melanoma tissues, cells or proteins isolated from the tissues do not meet the requirement of 35 U.S.C. 101.

If a molecule is to be used as a surrogate for a disease state some specific disease state must be identified in some way with the polynucleotide or polypeptide encoded there from. There must be some expression pattern or evidence of altered form that would allow the claimed polypeptides or polynucleotides to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one skilled in the art needs to know that the MrgX2 protein is present only in diseased tissue to the exclusion of normal tissue or present in diseased tissue at higher levels or in a different form from that present in normal tissues.

However, in the absence of any disclosed relationship between the protein expression and pathological condition, any information obtained in an effort to establish a differential expression pattern would constitute further research on establishing a specific, substantial, and credible utility for the method reliant on the presence of the MrgX2 protein in melanoma tissue or cells. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing". Therefore, without objective evidence that the binding of an antibody to MrgX2 protein (SEQ ID NO: 4) expressed on melanoma tissue or cell is indicative of some skin cancerous condition, the instant claims lack a specific, substantial, and credible asserted utility.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11, and 17-22 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The response filed 12/27/06 has been carefully considered but is deemed not to be persuasive. Applicant argues that *based on the teaching of specification on MrgX2 mRNA is exclusively expression in melanoma cell lines, and not in other tissue, one skilled in the art would recognize that any amount of MrgX2 protein is detected in a tissue sample, that tissue sample necessarily expression MrgX2 mRNA must be cancerous because expression of a protein requires that the mRNA encoding the protein be expressed first (page 6, 2nd para)*. Applicant, then, concludes *that one skilled in the art would recognize that because MrgX2 mRNA is not present in normal tissues and cells, MrgX2 protein can not be expressed in normal tissues or cells, thus, MrgX2 protein can only be present in disease tissues, to the exclusion of normal tissue (page 6, 2nd para)*. In response to this argument, the Office agrees with the applicant's conclusion that no mRNA would result in no protein in said tissues or cells only at the condition that the half life of the coding mRNA is longer enough for the detection by a known method used in the art. However, the Office does not agree with applicant, that there must be a detectable protein in the cancer tissues if mRNA is detected in said tissues. The reason has been discussed in the office action and again above, a level of mRNA expression is NOT always correlated with the level of its coding protein in the same tissues or cells, the Office have given examples above. Instant claims recite a method of diagnosing skin cancer by determining the MrgX2 protein expression using antibody to MrgX2

protein. If the levels of the protein in normal or disease condition are not known, how can one skilled in the art practice the method using an antibody to the protein for detection? In addition, the instant applicant does not provide any information on the levels of either mRNA or protein in the NORMAL skin tissue compared to melanoma tissues. One skilled in the art has known that expression of a specific protein in a specific cell line may not represent the pattern of tissue expression in normal or pathological condition because during the process of cell line development, overexpression of particular protein could and will occur. Thus, in order to claim a method having a specific, substantial utility for diagnosis purpose, applicant must provide evidence to support claimed invention for one skilled in the art, who could practice or use the method without further research or undo experimentation.

The utility, especially substantial utility, *by definition*, is a utility that defines "real world" use, and a utility that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility. In this case, the MrgX2 mRNA expression in melanoma cell lines suggests a potential for association with skin cancer and for diagnosis purpose, which, at the most, is an interesting invitation for further research and confirmation as it is not a practical method for "real world" use, and it requires significant further research and experimentation in order to form a useful and practical diagnosis method, which, by no means, is a routine or conventional experimentation. These further research and experimentation, however, is part of the act of invention, and until it has been undertaken, the claimed invention is not considered substantial.

In *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), the Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. ... a patent is not a hunting license. ... [i]t is not a reward for the search, but compensation for its successful conclusion.

Applicant also argues that if the case of expression of MrgX2 mRNA is not necessarily express the protein, it would be still true that the binding of an antibody to MrgX2 protein expressed on tissue or cells indicates skin cancer because mRNA is not present in normal tissues and cells. What is being

claimed is a method for identifying skin cancer, not methods for identifying healthy cells. Again applicant argues that based on applicant's disclosure, the skilled artisan would understand that the MrgX2 protein can only be present in diseased tissue to the exclusion of normal tissue (page 7). In response to this argument, again, claimed method are drawn to diagnosing skin cancer comprising determining MrgX protein by contacting tissue sample with antibody binding to MrgX2 protein expressed in the skin cancer. The specification neither provides the protein levels in skin cancer tissues comprising melanoma tissue compared to the normal tissues, nor provides the direction or guideline of correlation the level of mRNA to the level of the protein in those tissues. Thus, Applicant has NOT provided objective evidence that binding of an antibody to MrgX2 protein expressed on a tissue or cell is indicative of skin cancer. Therefore, based on the applicant's disclosure, one skilled in the art would conclude claimed invention is not supported by either a specific, substantial, and credible asserted utility and therefore, one skilled in the art would not know how to use the claimed invention. **Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for reason of the record.**

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600